Editorial

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Glycine Reuptake Inhibitors in the Treatment of Negative Symptoms of Schizophrenia

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ABSTRACT:

Glycine reuptake inhibitors in the treatment of negative symptoms of schizophrenia

Negative symptoms are present in over one quarter of patients with schizophrenia and are detrimental to prognosis, functionality and quality of life. Currently, the treatments for primary negative symptoms are inadequate. However, enhancing N-methyl-D-aspartate receptor hypofunctioning with glycine reuptake inhibitors has garnered optimism as a potential treatment. Trials of sarcosine-derivatives have yielded mixed results and potential severe side effects have halted progress to larger studies. Non- sarcosine derivatives such as bitopertin have proven to be less toxic and have shown success in phase II trials. Unfortunately, phase III trials of bitopertin to date have not met primary endpoints and a void in effective treatment options for negative symptoms persists. Further research to improve psychiatric study design, discover clinical biomarkers and build on early successes of other potential pharmacologic molecules is required.

Keywords: bitopertin, sarcosine, glycine reuptake inhibitors, schizophrenia

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INTRODUCTION

Schizophrenia (SZ) is a complex mental illness that is associated with positive, negative and cognitive symptoms. The negative symptoms of SZ are defined by the DSM-5 to be symptoms of expressive deficits and avolition, which carry a large burden of illness, poor prognosis and large cost to society[1-4]. The antipsychotic drugs currently available are, for the most part, inadequate treatments for the negative symptoms of SZ. The 2011 Guidelines of the British Association of Psychopharmacology suggest first a trial of a second generation antipsychotic (SGA) and then the addition of antidepressant therapy to treat concomitant primary depressive symptoms[5]. The SGAs are generally stronger antagonists of 5-HT2 receptors than of dopamine receptors, and some success with these drugs relative to the first generation antipsychotics has been reported, but a large proportion of patients with SZ do not respond adequately even to the SGAs[6].

In the search for a biochemical basis for SZ, the focus for many years was on the dopamine system[7-9], and indeed hypotheses related to this neurotransmitter system have played an important role in the development of antipsychotic drugs. However, it has become obvious that other neurotransmitters or neuromodulators also play an important role, and for several years the excitatory amino acid glutamate has been the subject of considerable attention[10-12], with a focus

on the possible contribution of hypofunction of N-methyl-D-aspartate (NMDA) glutamate receptors to the symptoms of SZ. Early rodent and human studies with phencyclidine (PCP) and ketamine (both NMDA non-competitive receptor antagonists) have demonstrated a similar phenotype to SZ, including positive, negative and cognitive symptoms[13,14]. This theory of hypoglutamatergia was strengthened by experiments demonstrating decreased CSF glutamate levels in phenotypic models of SZ, clinical observations of the effects of ketamine and PCP in healthy subjects, reversal of PCP-induced hyperactivity in mice with NMDA receptor enhancement and neurochemical studies in rodents suggesting that glycine reuptake inhibitors act in brain structures (hippocampus and prefrontal cortex) thought to be implicated in SZ[15-18].

The NMDA receptor is an allosteric receptor requiring glutamate and the coagonists glycine or D-serine. In rat models, it has been shown that increasing the function of NMDA receptors alleviates positive and negative symptom SZ phenotypes. Investigated modalities to target the hypofunctioning NMDA receptor in SZ have included supplementing antipsychotics with ligands and inhibiting ligand reuptake[17,19]. Supplementing with glycine and D-serine was subject to early success in small trials but the Cognitive and Negative Symptoms In Schizophrenia Trial (CONSIST) trial showed no significant improvement in cognitive or negative symptoms; these molecules also show poor brain penetration, resulting in peripheral side effects at large doses[20-23].

Glycine reuptake inhibitors (GRIs) have been used to indirectly increase glycine in the synaptic cleft[18]. This review will focus on the data available for the effects of GRIs on symptoms of SZ, specifically primary negative symptoms. A literature search was performed using MEDLINE and Embase to find articles published up to June 2014 using MESH terms "bitopertin", "sarcosine", "glycine reuptake inhibitors" and "SZ." Abstracts and posters from the 29th CINP World Congress of Neuropsychopharmacology as well as clinical trial media releases were searched for the latest in unpublished data.

Glycine Transporter-1 Inhibitors: Sarcosine (N-methylglycine) Derivatives

Initial trials of GRIs were performed with sarcosine derivatives. Preclinical data from rat models demonstrated efficacy (17 and references and Tables therein). Small clinical trials yielded conflicting data, with promising results when measuring change in Positive And Negative Syndrome Score (PANSS) total scores, when sarcosine or its derivatives were add-on therapy in chronic SZ, but no significant between-group differences were observed when they were used as monotherapy in acute SZ (17 for review). Both types of experiments demonstrated minimal side effects. However, these drugs non-competitively bind to Glycine Transporter-1 (GlyT1) in glial cells, leading to prolonged increases in glycine levels in prefrontal cortex and the brainstem. Therefore, although few side effects were reported at the 1g and 2g per day dose in the studies listed, significant side effects, notably ataxia, hypoactivity and a fatal decrease in respiratory effort, may occur[17]. Further, recent studies have proposed high sarcosine serum levels as a prostate cancer risk factor[24,25]. Due to risk and modest effects in recent trials, large trials to develop sarcosine-derived GRIs have not been pursued[26].

Glycine Transporter-1 Inhibitors: Non Sarcosine Derivatives

Non-sarcosine derivatives are much more promising as they inhibit competitively and lead to fewer toxic side effects[27]. Due to the possibility of toxicity still present, only a few non-sarcosine GlyT1 inhibitors have been developed for clinical trials, the most promising of them being bitopertin (RG1678)[14]. The preclinical trials with these drugs are summarized in[17] and the clinical trials are summarized in[17] and Table 1 here.

In preclinical studies, bitopertin has proven to be effective in rat models to reverse PCP-induced

positive and negative symptoms of the SZ phenotype and it has good bioavailability in the brain with oral dosing in positive emission tomography (PET) studies in baboons[28]. Human PET studies with bitopertin have demonstrated an inverted U pharmacokinetic therapeutic window, and have provided evidence for ideal dosing of bitopertin to be 10mg orally and daily, with less pronounced but effective results at 30mg daily[29].

A proof of concept phase IIb trial conducted by Umbricht et al.[30] was designed to test bitopertin efficacy as add on therapy to patients stable on an SGA but with persisting negative symptoms at a dose not exceeding the equivalent of 6mg risperidone a day for 8 weeks of treatment, vs. placebo. This trial yielded significant improvement in Positive and Negative Symptom Scale (PANSS) scores for negative symptoms and in Personal and Social Performance scores for functionality.

While bitopertin was successful in the trial as add-on treatment, the next question was to investigate the possibility that bitopertin could reduce positive symptoms as monotherapy. A phase 2/3 trial of monotherapy with bitopertin in acute SZ vs. placebo and the positive control olanzapine was conducted. In this trial, the olanzapine treatment arm did not differ significantly from a large placebo effect in reduction of positive symptoms, so the trial was declared a failure. Bitopertin at 10mg and 30mg did not significantly affect PANSS negative scores compared to placebo, but also did not increase positive symptoms and was also found to be safe[31]. (Table 1)

A large phase 3 trial (n>3500) was recently started that includes three trials in patients with SZ with suboptimally controlled symptoms and three

Table 1: Summary of recent clinical trials with bitopertin. Results from clinical trials with sarcosine, glycine and cycloserine are summarized in a table in[17].

Molecule	Reference	Experimental system	Main findings
Bitopertin	[30]	Phase IIb proof-of-concept study of patients stabilized on SGA and randomized equally to 8 weeks of treatment with bitopertin (10mg, 30mg, or 60mg daily) or placebo as adjunct treatment, n=323.	There was a significantly greater decrease of PANSS NSFS from baseline in bitopertin 10mg and 30 mg groups vs. placebo. Response rate was significantly higher for bitopertin10 mg group vs. placebo and differences in CGI-I-N and PSP were significant for that dose group.
Bitopertin	[31]	Phase 2/3 trial of bitopertin monotherapy compared with placebo in patients with acute exacerbation of SZ. Multicenter, randomized, double-blind, placebo and active- controlled, parallel group. 4 weeks or treatment and 4 weeks of follow up with bitopertin (10mg or 30mg daily) or olanzapine (15mg daily) or placebo as monotherapy, n=299 inpatients.	No statistically significant change from baseline in PANSS negative score of olanzapine or bitopertin (both doses) vs. placebo. Active control of olanzapine failed to statistically separate significantly from placebo for PANSS positive subscale (therefore deemed a failed trial). Both doses of bitopertin were generally safe and tolerated. Surrogate measures of readiness for hospital discharge and positive symptom control were seen with bitopertin 30mg dose.
Bitopertin	[32-34]	Three phase 3 double-blind, placebo-controlled studies evaluate the efficacy and safety profile of bitopertin when added to antipsychotic medicines in adults with sub-optimally controlled symptoms of SZ, 12 weeks, n>1000.	In progress until ~2016. Two of three trials were discontinued due to not meeting primary endpoints of PANSS NSFS.
Bitopertin	[35-37]	Three phase 3 double-blind, placebo-controlled studies evaluate the efficacy and safety profile of bitopertin when added to an antipsychotic in adults with persistent, predominant negative symptoms of SZ, 24 weeks, n>1000.	In progress until ~2016. Two of three trials were discontinued due to not meeting primary endpoints of PANSS positive symptoms factor scores.

Abbreviations: PANSS NSFS=Positive And Negative Symptom Scale Negative Symptom Factor Score, CGI-I-N=Clinical Global Impression – Global Improvement of Negative Symptoms, SANS= Scale for Assessment of Negative Symptoms, HRQoL=Health Related Quality of Life, PSP=Personal and Social Performance scale, GAF=Global assessment of functioning, PCP=Phencyclidine, SGA=second generation antipsychotic.

trials in patients with SZ with persistent, predominant negative symptoms[32-37]. On April 15, 2014, Hoffman-LaRoche announced that two of the trials in each category have been discontinued due to failure to meet primary endpoints[38,39].

Future Research

An urgent need for adequate treatment of negative symptoms in SZ remains. The glutamatergic hypothesis has opened doors to new therapies and may account better for negative symptoms of SZ. Unfortunately, there has been limited success in trials of agents, including the GRIs such as bitopertin, to this point, and this represents an urgent need for future research targeted at further understanding the pathophysiology of SZ negative symptoms, at developing different molecules for treatment and improving study design.

Schizophrenia is currently diagnosed by standardized symptom criteria. However, numerous molecular neuroscience studies strongly suggest that SZ does not represent a disease with uniform pathogenesis[40]. Schizophrenia may represent a group of mental disorders that simply share common symptoms, and thus, is not likely to respond to one uniform drug. In recent fMRI studies, it has been demonstrated that brain structural correlates are very heterogeneous among individuals with negative symptoms of SZ[41]. Correlating neurotransmitters, fMRI findings, PET and other biomarkers and clinical data to better understand the disease will hopefully result in more homogenous research samples, more accurate results and perhaps more individualized treatment plans[42]. With that knowledge it would be easier to determine if patients presenting with early, predominantly negative symptoms or more severe negative symptoms require a larger dose of study drug for adequate effect[17,43] or if any specific antipsychotic is superior in combination with GRIs[44].

The reason why large trials investigating treatments for negative symptoms are difficult and have large placebo effects may also be due to study design flaws[45]. For example, although the PANSS scale has been proven to show good reliability, validity and ability to detect change, it relies on evaluating differences in symptom categories like social withdrawal and abstract thought in a clinical interview and is ultimately less accurate than measuring a biomarker[46]. Further, the large studies currently lack long term measures that could be clinically significant, and development of these outcome parameters would be of benefit[47].

Even though there has been over two decades of research into the glutamatergic hypothesis as a target to treat negative symptoms, there is no loss of momentum in the field. Many promising small trials exist showing efficacy for negative symptom treatment, e.g. memantine as an augmentation strategy to clozapine[15], N-acetyl cysteine (NAC)[48], sodium nitroprusside[39,49], sodium benzoate[44,50] and a new agent based upon olanzapine linked to a sarcosinyl moiety (PGW5)[51].

Glycine reuptake inhibitors remain promising treatments despite recent setbacks. As the field of psychiatric research and understanding of SZ evolves, further trials will be needed to fill the unmet need for treatment of negative symptoms of SZ.

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